Testimony
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International Research Ethics: 10 Developments in 10 Years

Background

In April 2001, NBAC submitted to President Clinton its report *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, one of the first extended discussions by a government advisory group on this topic in the world. Exhaustive but not comprehensive, the NBAC report identified several key ethical and policy issues facing researchers, institutions, regulators, sponsors and others and made a number of recommendations to address them. This commission's staff have assessed the extent to which these recommendations have been implemented.

In the decade since, a comprehensive literature has emerged documenting a number of developments in the international health research and research ethics landscape including: the amount research conducted (by whom/where), developments in ethical guidelines and oversight mechanisms, the maturation of several difficult ethical issues, the emergence of new topics, and examples of excellence.

These developments should be seen in the context of certain world events since 2001 which ought to affect any assessment of international health research ethics: 9/11, two U.S. wars (among many others), an international economic collapse, the public health responses to SARS and pandemic influenza, and several natural disasters.

In my remarks this morning I'd like to highlight 10 of these developments in the past 10 years; although they are from my own personal list, all are supported by the literature.

Volume of International Health Research Has Grown; Locations Have Shifted

Number of international clinical trials conducted has increased, as has the number of research subjects enrolled in studies around the world
Number of FDA-sponsored studies has grown
Number of investigators working in other countries filing applications for INDs in the US has increased
Number of countries in which research is undertaken has expanded, with more growth in economically developing countries than developed countries

Changing geography of research calls for attention to social, cultural and political issues
Places greater emphasis on the ethical justification for conducting research in a country other than that of the PI?
Expansion calls the question that research is not motivated solely by science/ health/ global inequality, but rather by interest in countries with lower barriers to entry.

More Funding from More Sources

More money being spent by NIH; more foreign awards made
More money being spent by pharmaceutical companies (and more by these companies than by federal governments)
More money being spent by philanthropies and charities
More money being spent by U.S. NGOs
More foreign aid (some of which in the form of support for health research)

Not only does money influence the conduct of research (feasibility), but also how priorities get set and by whom.
A decade ago we were struck by the injustice of the 10/90 gap – that only 10% of health research spending went to diseases that affected 90% of the world.
Some funding for rare/neglected diseases, but this gap still substantially exists.

Innovative Arrangements for Conducting and Sponsoring Research

More public/private partnerships that extend beyond the traditional federally-sponsored (or pharmaceutical company-sponsored) trials
Use of prior agreements in the pre-trial setting has become a more common arrangement, and are now being used more regularly in research partnerships
Innovative funding arrangements (including humanitarian programs) are lowering

the cost and increasing access to previously unaffordable drugs

These new arrangements are changing the nature and scope of collaboration, and the attendant power relationships between sponsors and countries
Egalitarian partnerships are not only possible but working.
The involvement of larger organizations is changing the structure of the debate about access and cost of drugs.

Growth of Community Engagement Practices

CE has become an active area of scholarship and given rise to a number of exciting experiments -> ten years ago this was a foreign concept, now it is expected
Evidence can be found in greater involvement of communities in research design, explicit use of community advisory boards and committees, and more representation by non-affiliated members of these groups
Many guidelines have been updated to include engagement as an expectation

The traditional model of informed consent (one person being given information by one researcher) is becoming less common in international research:
barazzas in Kenya; deliberative democracy strategies in Western Australia biobanking and other examples
Too early to tell whether these models improve process and outcome of research, but there is potential for growth and innovation.

Harmonization Debate Has Evolved, Stalled, Evolved

More **countries** have developed (or substantially updated/revised) their own national guidelines;
More **specialized guidelines** developed including: embryonic stem cell research, public health research, biobanks, privacy protection, genetics
More **international and transnational organizations** (e.g., UNESCO, WHO, CIOMS, WMA, ICH) developed and/or regularly update their guidelines
Proposals to take advantage of the "equivalent protection" provision of US regulations have yet to be taken up, which may be read as a rebuff of national sovereignty

Whereas a decade ago, we were reminded about the ethical peril of applying a "double standard" to research, we may now be approaching a situation where multiple standards exist – and may divide along regional or national lines.
Ironically, the growth of policy documents in more countries has made it harder to achieve consensus on substantive matters of ethical acceptability.

The fact that more countries have FWAs with the US may alter the "sovereignty" argument.

Standard of Care Debate has Matured, But Consensus Not Achieved

Initial debates following the controversial ACTG 076 study focused on which standard ought to be adopted (highest possible vs. local standard)
Later debates appreciated that while "highest possible" might be morally preferred, it was often unattainable
Suggestions for compromise are now being made: high – but not highest – standard supplemented by other requirements to ensure benefit

The debate has matured beyond ideological extremes, to a point where legitimate efforts to find accommodation are being sought.
Would we be having the same discussion about the ACTG 076 study if the proven standard of care was an affordable one?

Deeper Understanding of Key Ethical Issues and Principles

The necessary set of ethical principles
Is agreement possible (or needed)?
The export of Belmont is less an instance of "US imperialism" than in the past
Longstanding principles continue to be debated
Minimizing exploitation, Clinical equipoise, Minimal Risk, Privacy, Scientific Validity
Informed Consent
the possibility of community consent
consent involving women
consent under extreme conditions; research during war-time; natural disasters
Newer principles proposed
Responsiveness to health needs as a justification for conducting research in another country
Fair benefits has emerged as a key issue in negotiations between sponsors and host countries
Solidarity
Community
Reciprocity
Social value

We lack consensus about the list of necessary and sufficient principles.
Attention focused on whether/how, in international settings in particular, principles beyond Belmont are identified and applied.
There is more empirical, legal, and social knowledge on how these principles

are used and interpreted.

Procedures and Policies for Ethics Review Have Evolved

More ethics review committees in more locations;
While "local" ethics review remains the dominant model for assessing the ethical acceptability of protocols, **other models** are being proposed:
regional IRB (Emanuel), central IRB (NCI) ; "ethics review systems" (Hyder);
Joint IRB (Meslin)
Foreign institutions now are negotiating and receiving Federalwide Assurances through OHRP
Efforts at benchmarking, evaluation, impact have been proposed
Emanuel's benchmarks "What Makes research Ethical?"
AHHRP's accreditation efforts
Institute of Medicine, OIG

The expansion of ethics review committees reflects a trend towards national efforts to assess and review protocols; also reflects a recognition that "dual" review continues to be an important principle in collaborative studies
However, expansion of committees has not yet resulted in a concomitant expansion of training and expertise to review international studies
Efforts to assess impact are an active area of study, consistent with the new philosophy of funding bodies to show impact/return on investment

Research Ethics Capacity Building has Expanded; Impact Still to Be Assessed

Dedicated training programs have emerged and expanded
Fogarty International Center's bioethics training program is well respected
More trainees in more countries in more positions
UNESCO, WHO, Welcome Trust, Gates Grand Challenges all recognize importance of building bioethics research capacity as **part of building science capacity**
European Union's European and Developing Countries Clinical Trial Partnership; Genome Canada's GEL3S program
Collaborative Institutional Training Initiative (CITI) reflects growth in on-line training
Bioethics commissions have grown, many of which offer advice on ethical and policy issues in research
Summit of National Bioethics Commissions is now a regular activity
More journals publishing more of these studies

More training ensures more individuals knowledgeable about research ethics throughout the world with more access to more resources

The role of the internet, web, Skype as an instrument of global learning has "expanded the classroom"
There remain questions about impact of training on effectiveness of review; protection of human subjects

Examples of Excellence -- U.S. has an opportunity to Learn from Others

IU- Moi Academic Research Ethics Partnership
Inter-Fogarty collaborations
McLaughlin-Rotman Center, University of Toronto: biotechnology and innovation research
Growing network of WHO collaborating centers in ethics
Willingness in many countries to take up issues even if there are few instantiations of the issues in local research (biobanking and genetics research)
Greater attention to ethics and public health research
Innovative and forward-looking guideline development
Canada: research on indigenous populations is one of the international gold standards

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The capacity to obtain this data was not possible ten years ago (e.g., clinicaltrials.gov; Centrewatch)

Eric M. Meslin/PCSBI March 1, 2011